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PCT/EP99/05073

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 28 March 2000 (28.03.00)	
International application No. PCT/EP99/05073	**Applicant's or agent's file reference** Le A 33 187-PC W1
International filing date (day/month/year) 16 July 1999 (16.07.99)	**Priority date** (day/month/year) 29 July 1998 (29.07.98)
Applicant STRAUB, Alexander et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

10 February 2000 (10.02.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer R. E. Stoffel
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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference Le A 33 187-PC W1	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP99/05073	International filing date (*day/month/year*) 16 July 1999 (16.07.99)	Priority date (*day/month/year*) 29 July 1998 (29.07.98)
International Patent Classification (IPC) or national classification and IPC C07D 471/04, 403/04, A61K 31/505 // (C07D471/04, 231:00, 221:00)		
Applicant BAYER AKTIENGESELLSCHAFT		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10 February 2000 (10.02.00)	02 November 2000 (02.11.2000)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP99/05073

I. Basis of the report

1. This report has been drawn on the basis of (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

☐ the international application as originally filed.

☒ the description, pages 1-87, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____.
pages _____, filed with the letter of _____.

☒ the claims, Nos. 1-18, as originally filed,
Nos. _____, as amended under Article 19.
Nos. _____, filed with the demand,
Nos. _____, filed with the letter of _____.
Nos. _____, filed with the letter of _____.

☒ the drawings, sheets/fig 1/2-2/2, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____.
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1 - 18	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1 - 18	NO
Industrial applicability (IA)	Claims	1 - 18	YES
	Claims		NO

2. Citations and explanations

This report makes reference to the following documents:

D1: WO-A-98/16507 (BAYER AG) 23 April 1998, mentioned in the application

D2: WO-A-98/23619 (BAYER AG) 4 June 1998, mentioned in the application

2.1 Novelty (PCT Article 33(2))

2.1.1 The subject matter of Claim 1 of the present application is substituted and optionally annelated pyrazole derivatives which carry in position 3 of the pyrazole ring a pyrimidine ring which is always substituted with a cycloalkyl group (all the examples contain cyclopropyl radicals). The technical feature added to the prior art consists in the replacement of alkyl groups known as substituents (see, for example, D1, page 144, Example II/42) by cycloalkyl groups (cf. the compound according to Claim 1 of the present application wherein A stands for phenyl, R^1 for 3-cyclopropyl, X and Y both stand for hydrogen and R^2 and R^3 together stand for an unsubstituted annelated benzene ring). Thus, dependent product Claims 2 - 5, and Claim 6 (method for the preparation of the final products), and the remaining Claims 8 - 18, which relate to

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(Continuation of V.2)

the use of the claimed compounds as medicaments or to the preparation of medicaments, are likewise novel within the meaning of PCT Article 33(2).

2.1.2 The amidine derivatives of Claim 7 are intermediate products for the preparation of final products of Claim 1. The hydroxamides of formulae (III - XXVII) disclosed in D1 (cf. page 223) which are used as intermediate products for the preparation of pyrazole derivatives which carry an oxadiazole ring instead of a pyrimidine ring in position 3 of the pyrazole ring can be considered to be the structurally closest compounds (cf. page 171, Example III/128, method of preparation J3). Consequently, the subject matter of Claim 7 meets the requirement of novelty (PCT Article 33(2)).

2.2 Inventive step (PCT Article 33(3))

2.2.1 Claim 1 of the present application comprises substituted (annelated) pyrazole derivatives containing a pyrimidinyl ring in position 3 of the pyrazole unit and a $-CH_2-A$ group on N-1 for the treatment of cardiovascular diseases. Document D1, which is considered to be the closest prior art, discloses N-heterocyclylmethyl-substituted pyrazole derivatives (including annelated derivatives) which likewise carry pyrimidinyl radicals in position 3 of the pyrazole ring (cf. D1, pages 142 - 146, Examples II/37 - II/49, page 151 and 152, Examples II/63 - II/67) from which the subject matter of Claim 1 differs in that the 2-pyrimidinyl radical according to the application must always be substituted with a cycloalkyl group instead of an alkyl group (see, for example, D1, page 144, Example II/42) (cf. the compound according to Claim 1 of the

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(Continuation of V.2)

present application wherein A stands for phenyl, R^1 for 3-cyclopropyl, X and Y both stand for hydrogen and R^2 and R^3 together stand for an unsubstituted annelated benzene ring). The compounds of D1 are likewise used for the treatment of cardiovascular diseases (see page 40, third paragraph).

2.2.2 The technical problem to be solved by the present invention would therefore appear to be to provide further annelated pyrazole derivatives for the treatment of cardiovascular diseases.

2.2.3 The solution proposed in Claim 1 of the present application cannot be considered to be inventive (PCT Article 33(3)) for the following reasons: Document D1 describes a wide range of possible substituents in the substitution pattern on the 6-membered heterocycle in position 3 of the pyrazole ring; no direct reference is made to cycloalkyl groups as possible substituents, but according to D1, phenyl and even functional groups can be taken into consideration as well as alkyl groups without impairment of the biological activity (cf. D1, Claim 1, definition of R^1). In document D2 also, in which pyrazolo[3,4-b]pyridines or indazole derivatives, substituted *inter alia* with pyrimidinyl groups in position 3 of the pyrazole unit, are presented as agents for the treatment of cardiovascular diseases, the substitution of the heterocyclic ring in position 3 of the condensed pyrazole ring is left fairly open (cf. D2, page 6). A person skilled in the art would therefore regard the incorporation of the cycloalkyl group instead of an alkyl or phenyl group in the compounds described in D1 as a conventional alternative measure for solving the technical problem of interest, for which measure an inventive step is

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not required, although no direct reference to the possibility of using cycloalkyl groups as substituents is made in the prior art.

2.2.4 This type of minor structural modification of a group of already known prior art compounds with identical biological properties can, however, only be considered to be inventive if the use of the distinguishing structural feature mentioned in 2.1.1 produces unexpected effects or properties compared with the already known compounds. However, no such effects and properties are mentioned in the application; a biological comparative test comparing the structurally closest compounds of D1 with compounds according to Claim 1 of the present application, for example, would be suitable for demonstrating unexpected properties (cf. item 2.1.1).

2.2.5 Dependent product Claims 2 - 5, and Claim 6 (method for the preparation of the final products), and the remaining Claims 8 - 18, which relate to the use of the claimed compounds as medicaments or to the preparation of medicaments, do not contain any features which, in combination with the features of any one of the claims to which said claims refer, meet the requirements of the PCT with regard to inventive step.

2.2.6 Claim 7 relates to intermediate products which are to be used for the preparation of final products according to Claim 1. An inventive step of intermediate products is present only if said intermediate products directly yield **inventive** final products, and if they have the same distinguishing structural feature as the final products, or if they are necessary at least for the preparation of end

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(Continuation of V.2)

products which meet the requirement of inventive step, that is if they first permit the preparation of said final products. Since no proof of an inventive step of the final products in the present case has been furnished, the claimed intermediate products are automatically not considered to be inventive within the meaning of PCT Article 33(3).

2.3 Industrial applicability (PCT Article 33(4))

The pyrazole derivatives of Claim 1 can be used in the preparation of medicaments for the treatment of cardiovascular diseases.